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EXAMINER

LE, EMILY M

ART UNIT PAPER NUMBER

1648

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/965,116

Applicant(s)

KANDIMALLA ET AL.

Examiner

Emily Le

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11/21/05+01/13/2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 7, 8 and 39-43 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 7, 8 and 39-43 is/are rejected.
- 7) ☒ Claim(s) 3 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/13/2006 has been entered.

### ***Status of Claims***

2. Claims 4-6 and 9-38 are cancelled. Claims 1-3, 7-8 and 39-43 are pending and under examination.

### ***Claim Objections***

3. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 3 fails to further limit claim 1 for the following reason(s):

Claim 3 depends on claim 1, wherein claim 1 specifically limits the pyrimidine nucleoside to one of the following: 5-hydroxymethyl cytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil. However, claim 3 does not further limit the pyrimidine nucleoside to the ones recited in claim 1. Instead, claim 3 is directed to encompass a genus of pyrimidine nucleosides that are dictated by the generic structural characteristics that are encompassed by the pyrimidine nucleosides recited in claim 1. In the instant, claim 3 is directed at a genus of pyrimidine nucleosides, whereas, the

claim from which claim 1 is directed at specific species of pyrimidine nucleosides.

Thus, claim 3 fails to further limit claim 1.

***Claim Rejections - 35 USC § 101***

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-3, 7-8, and 40-43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to immunostimulatory oligonucleotide compounds, wherein the compounds are required to have the following structural characteristics: a pyrimidine bonded to purine, wherein the pyrimidine is selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine and 4-thiouracil.

The pyrimidines recited in the claims exist in nature. And purines such as adenine and guanosine are also known to exist in nature. The claims do not contain any language that would imply that the claimed immunostimulatory oligonucleotide compounds are "man-made", isolated from nature or not products of nature. Thus, the claims are directed to encompass naturally occurring products. Hence, in view of the breadth of the full scope of the claims, the claims are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, naturally occurring immunostimulatory oligonucleotide compounds.

To overcome this rejection, the Office suggests that Applicant amends to claims to include the term "isolated".

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 7-8 and 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims refer to 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine and 4-thiouracil as non-natural pyrimidines. This reference renders the claims indefinite because 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine and 4-thiouracil are known to exist in nature. For example, 4-thiouracil exists in seeds of brassica and crucidera species; and 5-hydroxymethylcytosine is found in *Escherichia coli* phage T4 DNA. Thus, since these pyrimidine compounds are naturally occurring, then, it is unclear what is intended by the recitation "non-natural".

Additionally, the claims are rendered indefinite because of the recitation, "non-natural purine nucleoside". It is unclear what is encompassed as a non-natural purine nucleoside. For instance, adenine, guanine, hypoxanthine and xanthine are all purines, however, are they "non-natural"?

Furthermore, the recitations "anaiog" and "derivatives" also render the claims indefinite because scope of the subject matter embraced by the cited recitations is unclear.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 7-8 and 42 are rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz.<sup>1</sup>

In response to the rejection set forth in the record, Applicant submits that Schwartz does not envisage the use of arabinose as a possible sugar analog for C nucleoside in a CG dinucleotide.

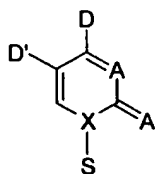
Applicant's submission has been fully considered, but it is not persuasive. Schwartz teaches modifying the dinucleotide CG with a modified C, wherein C is cytosine. The modified C that Schwartz teaches is cytosine arabinoside, as evidenced by lines 5-15 of page 13 and claim 4 of Schwartz. At lines 5-15 of page 13, Schwartz suggests that the modified cytosine can be aracytosine. In addition to merely suggestion the specified modification, Schwartz clearly envisaged the modification, as evidenced by claim 4 of Schwartz et al.

The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a nucleoside selected from the

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group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2-deoxyguanosine or a guanosine analog.

Claim 3 also requires that the pyrimidine be linked to the purine via an internucleotide linkage selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate; the pyrimidine nucleoside has the formula (I):



(I)

wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine.

The claims, claims 7-8 and 42 also require the pyrimidine nucleoside to comprise a non-naturally occurring sugar moiety, which is later limited to arabinose or arabinose derivatives; which is later specified as aracytosine.

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<sup>1</sup> Schwartz, David. WO 99/62923, Published December 19, 1999.

Schwartz teaches an immunomodulatory oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine aracytosine and purine is guanosine, and the pyrimidine is linked to the purine via an internucleotide linkage, phosphodiester.

The oligonucleotide compound of Schwartz comprises aracytosine. Aracytosine is not a cytidine or deoxycytidine. Aracytosine has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. The pentose sugar ring of aracytosine is a non-naturally occurring sugar moiety, arabinose. [See claim 4 of Schwartz]

In the instant, Schwartz teaches the same oligonucleotide compound as that instantly claimed. Ergo, Schwartz anticipates the claimed composition.

10. Claims 1-3, 7-8 and 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Nguyen et al.<sup>2</sup>

The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2'-deoxyguanosine and a guanosine analog. The claims require the pyrimidine be linked to the purine via an internucleotide linkage

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<sup>2</sup> Nguyen et al. Modification of DNA duplexes to smooth their thermal stability independently of their base content for DNA sequencing by hybridization. Nucleic Acids Research, 1997, Vol. 25, No. 15, 3059-3065.



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selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate.

Claim 3, which depends on claim 1, requires the pyrimidine nucleoside to have the formula (I):



wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine. Claim 7, which depends on claim 1, requires the pyrimidine nucleoside to comprise a non-naturally occurring sugar moiety, which is later limited to arabinose or arabinose derivatives by claim 8, which is later specified as aracytosine by claim 42. Lastly, claim 41, which depends on claim 1, limits the pyrimidine to N4-ethylcytosine.

Nguyen et al. teaches several oligonucleotide compounds comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is linked to the purine via a phosphodiester. The oligonucleotide compounds of Nguyen et al. are at

least 6 nucleotides in length. [First full paragraph, left column on page 3061; Figure 2, and Tables 1-3.]

The pyrimidine nucleoside present in one of the oligonucleotide compound of Nguyen et al. is aracytosine, wherein the aracytosine is linked guanosine. The pentose sugar ring of aracytosine is a non-naturally occurring sugar moiety, arabinose. Aracytosine is not a cytidine or deoxycytidine, and have a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. And this particular oligonucleotide compound comprises guanosine.

The other oligonucleotide compounds that Nguyen et al. teaches comprise N4-ethylcytosine as the pyrimidine, wherein the N4-ethylcytosine is linked guanosine and a guanosine analog (adenine), separately. N4-ethylcytosine is not a cytidine or deoxycytidine, and have a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a hexose sugar ring, and X is nitrogen.

In the instant, Nguyen et al. teaches oligonucleotide compounds that are the same as those instantly claimed. The oligonucleotide composition of Nguyen et al. has the same structural characteristics as the claimed invention.

It is recognized that Nguyen et al. does not comment on the immunostimulatory activity of the oligonucleotide compounds that Nguyen et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: "[T]he discovery

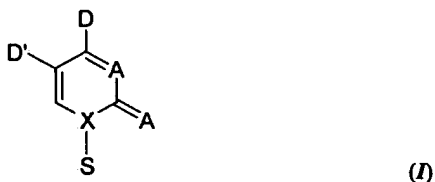
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of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)". Hence, Applicant's discovery of a previously unappreciated property, the immunostimulatory property of the oligonucleotide compounds of Nguyen et al., of the prior art composition does not render the old composition patentably new to the Applicant. Thus, the claimed composition is anticipated by the oligonucleotide compound of Nguyen et al.

11. Claims 1-3 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Clivio et al.<sup>3</sup>

The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2'-deoxyguanosine or a guanosine analog. The claims also require the pyrimidine to be linked to the purine via an internucleotide linkage selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate.

Claim 3 requires the pyrimidine nucleoside to have the formula (I):



wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine. Claim 43 later limits the pyrimidine nucleoside to 4-thiouracil.

Clivio et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is linked to adenine, a guanosine analog, via a phosphodiester. [First full paragraph of page 67.] The oligonucleotide compound of Clivio et al. is at least 6 nucleotides in length. The pyrimidine nucleoside present in the oligonucleotide compound of Clivio et al. is 4-thiouracil. 4-thiouracil is not a cytidine or deoxycytidine, and has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. In the instant, Clivio et al. teaches an

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<sup>3</sup> Clivio et al. Synthesis and purification of oligonucleotides containing sulfur substituted nucleobase: 4-

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oligonucleotide composition that is the same as those instantly claimed. The oligonucleotide composition of Clivio et al. has the same structural characteristics as the claimed invention.

It is recognized that Clivio et al. does not comment on the immunostimulatory activity of the oligonucleotide compound that Clivio et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)". Hence, Applicant's discovery of a previously unappreciated property, the immunostimulatory property of the oligonucleotide compound of Clivio et al., of the prior art composition does not render the old composition patentably new to the Applicant. Thus, the claimed composition is anticipated by the oligonucleotide compound of Clivio et al.

12. Claims 1-3 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Tardy-Planechaud et al.<sup>4</sup>

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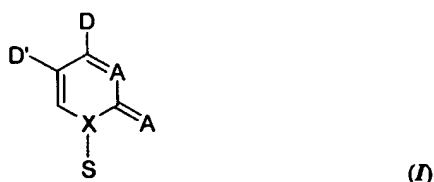
thiouracil, 4-thiothymine and 6-mercaptopurine. *Tetrahedron Lett.*, 1992, Vol. 33, 65-68.

<sup>4</sup> Tardy-Planechaud et al. Solid phase synthesis and restriction endonucleases cleavage of oligodeoxynucleotides containing 5-(hydroxymethyl)-cytosine. *Nucleic Acids Research*, 1997, Vol. 25, No. 3, p. 553-558.

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The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a pyrimidine nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2'-deoxyguanosine or a guanosine analog. The claims also require the pyrimidine to be linked to the purine via an internucleotide linkage selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate.

Claim 3 requires the pyrimidine nucleoside to have the formula (I):



wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine. Claim 40 later limits the pyrimidine nucleoside to 5-hydroxymethylcytosine.

Tardy-Planechaud et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is linked to adenine, a guanosine analog via a phosphodiester. [Test sequence disclosed on page 555.] The oligonucleotide compound of Tardy-Planechaud et al. is at least 6 nucleotides in length. The pyrimidine nucleoside present in the oligonucleotide compound of Tardy-Planechaud et al. is 5-hydroxymethylcytosine. 5-hydroxymethylcytosine is not a cytidine or deoxycytidine, and has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. In the instant, Tardy-Planechaud et al. teaches an oligonucleotide compound that is the same as those instantly claimed. The oligonucleotide compound of Tardy-Planechaud et al. has the same structural characteristics as the claimed invention.

It is recognized that Tardy-Planechaud et al. does not comment on the immunostimulatory activity of the oligonucleotide compound that Tardy-Planechaud et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195

USPQ 430, 433 (CCPA 1977)". Hence, Applicant's discovery of a previously unappreciated property, the immunostimulatory property of the oligonucleotide compound of Tardy-Planechaud et al., of the prior art composition does not render the old composition patentably new to the Applicant. Thus, the claimed composition is anticipated by the oligonucleotide compound of Tardy-Planechaud et al.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claim 39 rejected under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al.<sup>5</sup> in view of Schwartz et al.

The claim is directed at an immunostimulatory oligonucleotide comprising a dinucleotide having the formula 5'-pyrimidine-purine-3', wherein the oligonucleotide is at least 6 nucleotides in length, and wherein the pyrimidine is 5-hydroxycytosine and the oligonucleotide further comprises a phosphorothioate internucleotide linkage.

Kreutzer et al. teaches an immunostimulatory oligonucleotide comprising a dinucleotide having the formula 5'-pyrimidine-purine-3', wherein the oligonucleotide is at least 6 nucleotides in length, and wherein the pyrimidine is 5-hydroxycytosine. [Page 3579 of Kreutzer et al.]

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<sup>5</sup> Kreutzer et al. Oxidized, deaminated cytosines are a source of C→T transitions *in vivo*. Proc. Natl. Acad. Sci. USA, 1998, Vol. 95, 3578-3582.



The difference between the teachings of Kreutzer et al. and claim 39 is: the immunostimulatory oligonucleotide of Kreutzer et al. does not comprise a phosphorothioate internucleotide linkage.

However, the deficiency noted in Kreutzer et al. is compensated by the teaching of Schwartz et al. Schwartz et al. teaches the use of phosphorothioate linkages in place of phosphodiester linkages. Schwartz et al. notes that phosphorothioate linkages can be more immunogenic than phosphodiester linkages, and are more resistant to degradation. [First full paragraph of page 12 of Schwartz et al.]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use phosphorothioate linkages. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to i) enhance the immunogenicity of the immunostimulatory oligonucleotide of Kreutzer et al., and/or ii) increase the half-life of the oligonucleotide of Kreutzer et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the modification of immunostimulatory oligonucleotides with phosphorothioate linkages is well practiced in the art.

### ***Conclusion***

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



E. Le



Jeffrey S. Parkin, Ph.D.  
Primary Patent Examiner  
Art Unit 1648